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Amebic Liver Abscess

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, CA 94143.

DR. SMITH:* *In this conference we will discuss amebic liver abscess, a subject prompted by the diagnosis in a patient recently seen on our medical service. We have asked Dr. Robert Goldsmith to review this entity for us.*

DR. GOLDSMITH:† Before discussing the diagnosis and management of amebic liver abscess, I wish to give a broader view of the disease. What is the prevalence of amebic liver disease in the United States today? How often is one likely to see it, and what syndromes might one encounter in association with it?

In a review of 166 surveys nearly two decades ago, Burrows estimated a prevalence rate for amebiasis in the United States of about 5 percent.[1] Because so few surveys have been conducted since then, relatively little is known about its current prevalence.[2-4] Higher rates are found in custodial institutions and under conditions of poor sanitation and crowding. Prevalence rates of 11 percent to 45 percent were reported from five mental institutions and of 2 percent to 24 percent from four Indian reservations.[4] Other groups at increased risk are immigrants, visitors and travelers from areas of the world that are highly endemic for amebiasis. The most important mode of transmission in the United States is transfer from person to person within households. Transmission by food handlers and by contaminated water is less common.[2-4] Recently, investigators have noted the frequent venereal transmission of amebiasis in homosexual men in urban areas; it is often accompanied by other enteric infections including giardiasis, hepatitis, shigellosis and nonpathogenic protozoa.[5]

Clinical Syndromes of Amebiasis

The clinical syndromes of amebiasis[6-10] are shown in Table 1. Asymptomatic and mild intestinal infections are seen more commonly; severe intestinal infection and hepatic abscess are less frequent. Ameboma and infections in other extraintestinal sites are rarely observed in patients in the United States.

Asymptomatic Infection

In practice one may diagnose an asymptomatic amebiasis infection as a result of examining the fellow household members or sexual contacts of a patient known to have amebic disease, or after examining asymptomatic persons recently returned from an endemic area abroad. Such asymptomatic cyst carriers should be treated because over the following few years symptomatic

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TABLE 1.—*Clinical Syndromes Due to Amebic Infections*

Intestinal
Asymptomatic intestinal infection
Mild intestinal infection (nondysenteric colitis)
Severe intestinal infection (dysenteric colitis)
Ameboma
Extraintestinal
Hepatic abscess
Infection of other tissues

TABLE 2.—*Pathologic Features of the Liver Caused by Amebic Infections*

Real Disease Entities
• Amebic liver abscess
Enlarged, painful, tender; fever
• Nonspecific hepatomegaly
Slight enlargement and tenderness associated with intestinal amebiasis
Theoretical Disease Entity
• Amebic hepatitis
Pathologic characteristics have not been documented

intestinal disease or a liver abscess may develop. Also, these carriers may be a source of infection for others. However, most asymptomatic persons will probably never become symptomatic, and eventually their infections will resolve spontaneously. Nevertheless, because of the possible existence of stable, nonpathogenic strains of *Entamoeba histolytica,* controversy continues over whether to treat asymptomatic infections.[11,12] Therefore, until laboratory means are found to identify such strains, it is prudent, in countries where pathogenic strains are endemic or frequently imported, to view all *E histolytica* isolates as potentially pathogenic.

A reminder—steroids and immunosuppressive drugs can cause severe exacerbations of quiescent intestinal amebic infections. Therefore, the disease should be thoroughly ruled out before these drugs are used to treat other conditions.

Mild to Severe Intestinal Infections

In a case of mild intestinal disease, the patient has a few bowel movements a day, which are free of blood or mucus. As the severity of the intestinal infection increases, the patient may have 10 to 20 or more bowel movements a day, with increasing amounts of blood, mucus and bits of necrotic tissue and decreasing amounts of fecal matter. In severe cases, patients often experience pronounced weakness, vomiting, high fever, weight loss and diffuse abdominal tenderness; frequently, they also have low-grade hepatic enlargement and tenderness.

Ameboma

I recall a patient seen in San Francisco about eight years ago. He was a 45-year-old man who had recently returned from Mexico. A roentgenogram of the large bowel showed an annular lesion. The working diagnosis was carcinoma. He was operated on, but died several days later. The final diagnosis was not carcinoma but ameboma and amebic peritonitis. Ameboma is an unusual manifestation of intestinal amebiasis in which a granulomatous reaction to *E histolytica* results in a stricture or tumor that may project into the bowel lumen or become an annular lesion. Amebomas are found in the large bowel, most often in the cecum or rectal areas; clinically and radiologically, they may resemble bowel carcinoma or tuberculosis.

I have described this patient's illness to emphasize the need, when taking a medical history, for asking questions about travel and residence: "Where have you traveled recently?" And, "Where have you lived in past years?" The responses may help to determine whether an exotic disease should be included in the differential diagnosis. Perhaps if the patient had been asked such questions, knowledge of his exposure to amebiasis while in Mexico might have suggested ameboma as a possible cause of a constricting bowel tumor.

Hepatic Amebiasis

I wish now to focus on amebic infection in the liver.

In appraising the liver's response to amebic infection, investigators have had a continuing controversy about the types and pathogenesis of lesions[8,9,13,14]: two disease entities have been clearly established, the third remains theoretical (Table 2). The real entities are amebic liver abscess and nonspecific hepatomegaly. The latter is a low-grade enlargement and tenderness of the liver that accompanies moderate to severe intestinal infection. The enlargement is probably a toxic response to the intestinal infection and is nonspecific. It is postulated that gut infection allows bacterial toxins or products of tissue destruction to gain access to the liver. The hepatomegaly is a nonspecific response because (1) findings of liver scans and biopsies are negative, and (2) when one treats the intestinal infection with luminal-specific drugs but does not treat the liver

infection with hepatic-specific drugs, the intestinal infection is eradicated and the liver enlargement and tenderness clear as well. The most frequently promulgated theoretical entity is amebic hepatitis, which is defined as the diffuse spread of trophozoites throughout the liver, causing microscopic inflammatory lesions. However, pathologic studies have failed to provide conclusive evidence for the diffuse spread of amebas or for the theory that the disease proceeds from a presuppurative, inflammatory lesion to an abscess. This contrasts with the accepted view that amebas survive and multiply in the liver, immediately causing focal hepatic necrosis as a result of their cytolytic activity, and that subsequently the microabscess enlarges concentrically.

Cardinal Features of Amebic Liver Abscess

Amebic liver abscess, although a relatively infrequent sequel to intestinal infection, is not uncommon given the large number of intestinal infections. An abscess may occur months to years after onset of intestinal infection, and often after intestinal symptoms have disappeared. Detectable abscesses range in size from small (about 2 ml) to massive (over 5 liters). They may be single or multiple, and they occur more often in the right lobe and in males.

For most patients the disease is an acute process; however, in a few it is a chronic indolent disease. In a review of 400 consecutive admissions for amebic liver abscess in Durban, South Africa, Adams reported that 59 percent of patients had acute symptoms (referable to the liver) for less than two weeks; only 5 percent had symptoms for more than 12 weeks. Concurrent intestinal symptoms were reported by 14 percent of the patients at the time they were seen, and 19 percent reported a previous history of dysentery.[8]

The cardinal signs and symptoms of amebic liver abscess are a continuous, dull to severe pain in the hepatic area, liver enlargement, intercostal or subcostal tenderness, and fever with temperatures of 39°C (102.2°F) or higher (Table 3). Pain may be felt in the epigastrium, and when the right diaphragmatic area is involved, the pain may be pleuritic or referred to the right shoulder. Typically, the pain is increased by percussion. Enlargement of the liver may be subcostal, or there may be a localized bulging of the rib cage. It may also present as a right subdiaphragmatic process: diminished movement of the diaphragm at fluoroscopy, dullness to percussion, reduced breath sounds, rales or a rub. Systemic symptoms including chills, night sweats and malaise may be present, and the patient is often prostrate. Rarely, a large abscess compresses the biliary outflow causing obstructive jaundice.

TABLE 3.—*Cardinal Features of Amebic Liver Abscess*

Signs and Symptoms	*Frequency (Percent)*
Pain	85- 99
Generalized enlargement of liver	75- 95
Intercostal or subcostal tenderness	75- 85
Fever, 39°C (102.2°F)	80-100
Prostration	50
Signs at right base	45
Gastrointestinal symptoms	5- 25
Epigastric tenderness	20
Chills and sweating	30- 60

TABLE 4.—*Typical Laboratory Findings in Patients With Amebic Liver Abscess*

Leukocyte count: 15,000-25,000 per cu mm (25% less than 10,000; 10% more than 25,000)

Eosinophilia: none

Normocytic, normochromic anemia: 50-80%

Abnormal liver function test results:
- Generally low-grade, no distinctive pattern
- Most common abnormalities: alkaline phosphate elevation, Bromsulphalein retention, and albumin/globulin reversal with normal total protein

E histolytica in stool: 12-18%

Aspiration of abscess contents: *E histolytica* found in 15-50%

Positive serologic test results: 95%

The composite findings suggest a clinical diagnosis of liver abscess, but they do not differentiate an amebic from a pyogenic abscess or rule out an infected cyst, hydatid or necrotic tumor of the liver. Amebic and pyogenic infections can occur concurrently in an abscess, perhaps in 2 percent to 3 percent of cases.

Without prompt treatment an amebic abscess may rupture into contiguous structures, particularly the pleural, peritoneal or pericardial spaces, or the lungs. Localized adhesions and widespread hematogenous dissemination may occur. Cachexia, secondary infection, shock and death may result.

The patient under discussion here had an illness of a week's duration, with continuous right upper quadrant abdominal pain referred to his right shoulder. Findings of radiologic studies showed a 7-cm lesion in the superior part of the right lobe of the liver. The diagnosis of amebic abscess was based on a positive serologic test re-

TABLE 5.—*Typical Laboratory Findings in Patients With Amebic Intestinal Infection*

Leukocyte count: may be elevated
Eosinophilia: none
Stool examination for *E histolytica:*
Probability of finding organism in infected patients after testing three specimens is 80% and after six specimens is 90%
Sigmoidoscopy:
Appearance of lesions; *E histolytica* in exudate and in biopsy specimen
Serologic test results:
Asymptomatic infection: less than 10% positive
Mild intestinal disease: 10-40% positive
Severe intestinal disease: up to 90% positive
In vitro culture: presence of *E histolytica*

TABLE 6.—*Enhancing Sensitivity of Stool Examination for* E histolytica

Collect specimens at two-day intervals (intervals of three to four days are preferable) in clean container free of urine and toilet water.
Preserve immediately by mixing well, one part with formalin, and one part with polyvinyl alcohol fixative.
Substances that may block detection (collection should be delayed 10 to 14 days after their use): antibiotics, mineral oil or castor oil, magnesium hydroxide or bismuth, kaolin compounds, and saline, soap, tap water or barium enemas.

sult, presence of *E histolytica* in the stool, a gallium scan of the liver compatible with an amebic lesion and a rapid response to treatment. However, the parasite was not found in the aspirate. This patient's condition could represent the occasional case of combined amebic and pyogenic infection. Pyogenic infection is suggested by the presence of many polymorphonuclear leukocytes in the aspirate and by its foul smell, a typical characteristic of pyogenic but not of amebic infections. No bacteria were cultured; however, the patient had been receiving antibiotics.

Laboratory Tests for Amebic Liver Abscess

Laboratory test results for this patient included a peripheral blood leukocyte count of only 15,000 per cu mm, which fits into the 15,000 to 25,000 range seen in about 65 percent of patients with amebic liver abscess (Table 4). Only about 10 percent of patients have leukocyte counts of over 25,000 and 25 percent have less than 10,000 per cu mm. Eosinophilia is not usually present, but most patients have a normocytic, normochromic anemia. Abnormal findings on liver function tests are frequent, but generally are low grade and of no distinctive pattern. The most common abnormalities observed are elevated levels of alkaline phosphatase in the serum, Bromsulphalein (BSP) retention and albumin-globulin reversal with normal total protein.

Additional diagnostic procedures that are useful include examination of stools for *E histolytica,* serologic testing and, for selected patients, aspiration of abscess contents to determine the causative organism. The parasite will be found in stool specimens in only about 10 percent of cases and in abscess aspirates in up to 50 percent of cases if very good techniques are used. Serologic test results will be positive for nearly all patients with the disease.

Laboratory Tests for Amebic Intestinal Infection

Although the leukocyte count may be elevated (but not to high levels), there is no eosinophilia in amebic intestinal disease (Table 5). The definitive test is detection of *E histolytica* in stool through meticulous examination. The procedure is lengthy and, therefore, costly, and unfortunately is not highly sensitive. Examination by skilled technicians of three stool specimens collected under optimal conditions from each patient known to have intestinal amebiasis will detect only about 80 percent of amebic infections. Three additional tests will raise diagnostic sensitivity to about 90 percent.[15]

For patients with amebic liver abscess, the likelihood of finding the organism in stool is only 12 percent to 18 percent. Our standard procedure is to collect three specimens at intervals of two days or longer, with one of the three specimens obtained after administration of a laxative. Intervals of three to four days are probably preferable. Specimens should be collected in a clean container without coming in contact with urine or toilet water. If the specimen cannot be brought to the laboratory within an hour, the patient should preserve it immediately by mixing one portion well with 10 percent formalin and another with polyvinyl alcohol fixative. (Polyvinyl alcohol is a poison; therefore, it should be provided in a child-proof bottle and labeled as such.) Specimen collection should be delayed 10 to 14 days if any of the substances listed in Table 6 have been taken orally because they often block detection of the organism.

Additional diagnostic tests for amebic intestinal infections include sigmoidoscopy, mucosal biopsy, serology and, when available, in vitro culture of

amebas. Although sigmoidoscopy is indicated for many patients with possible amebic liver abscess, frequently it does not contribute to the diagnosis because the intestinal phase of the disease may be minimal or have cleared. The procedure should not be preceded by a cleansing enema. In mild disease, tiny ulcers with normal surrounding mucosa may be seen. In severe disease, sigmoidoscopic findings may include edema, hyperemia, granular and friable mucosa, and large ulcers. Diagnosis depends on finding the organism in exudate obtained from the surface of the ulcers, or in exudate or liquid feces collected from the lumen. Specimens should be collected using a glass pipette (do not use a cotton swab), or by scraping the ulcer surface with a metal instrument. The material collected is used to prepare smears for direct wet examinations and for fixation in Schaudinn's solution. Some centers do mucosal biopsies routinely; the specimens are best examined by immunofluorescent methods. In vitro culture of *E histolytica* generally provides a low yield of positive results.

Radiologic and Nuclear Medicine Procedures

Routine radiologic films will show abnormalities in over 60 percent of patients. X-ray studies of the abdomen will frequently show hepatomegaly. X-ray films of the chest with lateral views may show elevation of the right hemidiaphragm, pleural effusion, basilar pulmonary infiltrates, atelectasis, or collapse and consolidation of the lung. By fluoroscopy the motility of the right hemidiaphragm may be reduced or abolished. Radioisotope liver scans, computerized tomography and ultrasound studies will usually make it possible to locate the lesion, determine its size and differentiate a solid from a cystic lesion. The gallium citrate scan may prove useful in differentiating an amebic from a pyogenic abscess.[16] The finding of increased gallium activity at the periphery of a large "gallium-negative" lesion has been described as aiding in the diagnosis of amebic abscess.[17] Barium meal and barium enema studies may be useful in showing changes in stomach contour and position, as well as pressure on the colon caused by an abscess of the left lobe of the liver. Invasive procedures such as arteriography are used infrequently.

Serologic Tests

A variety of serologic tests are both sensitive and specific.[2,3,18] If positive, they indicate current or past amebic infection and are, therefore, of greater usefulness in nonendemic areas. Antibody will be present only if there has been significant tissue invasion; thus, test findings are positive in over 95 percent of patients with amebic abscesses and 80 percent to 90 percent of those with severe intestinal infections. Generally, test results are negative in patients with asymptomatic intestinal infections. For tests that provide titers, the degree of seropositivity does not correlate well with severity of infection. In the United States two types of tests are commonly available: the indirect hemagglutination test at the Center for Disease Control in Atlanta (submit specimens through your local health department) and the agar-gel diffusion test which is carried out by local laboratories. The antigen is commercially available. The gel diffusion test, though somewhat less sensitive, is often of particular value because a report can be made available within 24 to 48 hours, when it is most needed in differential diagnosis of liver abscess or severe intestinal disease. The gel diffusion test becomes negative within two to three months of cure of liver abscess, but seroconversion by indirect hemagglutination test may take several years. Continuing asymptomatic intestinal infection is not ruled out by a negative gel diffusion test, but requires negative stool examinations as well. Two other tests available at some centers, counter current immunoelectrophoresis and cellulose acetate precipitin tests, can be conducted so rapidly that reports can be provided within hours. Further development of the enzyme-linked immunosorbent assay (ELISA) technique may permit detection of antigen in stool and in aspirates from liver abscesses.

Aspiration of Amebic Abscesses

The specific indications for aspirating an amebic abscess, and whether to do it percutaneously or during an exploratory surgical procedure continue to vary among authorities.[6,8-10,19-21] The main purposes of aspiration are to establish the diagnosis and to reduce the likelihood of rupture of a large abscess before drugs can be effective. Though it remains to be determined if evacuation of large lesions speeds their healing, it does immediately relieve pain and fever.

When the differential diagnosis between pyogenic and amebic abscess is in doubt, aspiration is indicated for diagnostic purposes.[6,8,9] Clinically diagnosed amebic abscesses, however, should not be aspirated for diagnostic purposes alone, be-

cause conservative medical management with a therapeutic drug trial is sufficient confirmation. However, if a good clinical response is not obtained within about three days, aspiration should be done. For large amebic abscesses, where there is danger of imminent rupture, most workers concur that aspiration is indicated for therapeutic purposes. The Durban group continues to aspirate amebic abscesses of all sizes if they can be reached percutaneously; this results in aspiration of about two thirds of their cases.[8] Nevertheless, it remains to be determined whether chemotherapy, in combination with aspiration of all abscesses, sufficiently reduces treatment failure rates to warrant the risks of the procedure.

An exploratory surgical operation is indicated (1) when inspection of a mass is needed before needling, (2) when an abscess that requires aspiration cannot be reached by a needle (especially abscesses of the left lobe) or if the needle fails to locate the abscess or (3) when under therapy the patient's condition is deteriorating or the quantity of pus is increasing. Repetitive puncture or punctures at multiple sites should not be done; drainage at laparotomy is safer.[9] The treatment of pyogenic abscess is surgical intervention with open and adequate drainage.[20]

Aspiration should be done under absolutely sterile conditions; the risks of the procedure are introduction of infection and hemorrhage; however, these risks are low. The patient should be mildly sedated and the skin anesthetized at the puncture site. Using radiologic studies as a guide for placement of the needle, enter at the site of greatest tenderness, or, if present, the point of skin edema or at the area of stony dullness to percussion. Use a number 20 needle equipped with a stop so the point can go no deeper than 8 cm to avoid inadvertent puncture of a portal radicle; change the direction of the needle no more than two to three times. When the abscess is located, change to a wide-bore needle and collect the fluid in aliquots. Only the final aliquot should be studied. Add to it 10 units of streptodornase per ml, incubate for 30 minutes at 35°C, centrifuge at 1,000 rpm for five minutes, and then examine both saline mounts and stained preparations. The aspirate should also be examined by Gram stain and cultured aerobically and anaerobically. The color of the fluid may vary from cream to yellow to green or chocolate. The fluid is relatively odorless in contrast to the foul smell of that from a pyogenic abscess.

TABLE 7.—*Partial List of Useful Antiamebic Drugs*

Tissue amebicides (act primarily in the bowel wall, liver or other extraintestinal tissues)
Dehydroemetine, emetine
Chloroquine (principally active in the liver)
Luminal amebicides (act primarily in the bowel lumen)
Halogenated hydroxyquinolines: diiodohydroxyquin, iodochlorhydroxyquin
Pentavalent arsenicals: glycobiarsol, carbarsone
Alkaloids: emetine-bismuth-iodide
Amides: clefamide, diloxanide furoate
Antibiotics (act also in bowel wall): tetracyclines, paromomycin
Tissue and luminal amebicides
Metronidazole

Differentiation of Amebic and Pyogenic Liver Abscess

Amebic and pyogenic liver abscesses are difficult or even impossible to differentiate[20,21] either

TABLE 8.—*Treatment of Amebic Liver Abscess*

Drug(s) of Choice	*Alternative Drug(s)*
(1) Metronidazole, 750 mg three times per day for 10 days,	(1) Dehydroemetine,* 1 mg/kg of body weight per day intramuscularly or subcutaneously for 10 days (maximum daily dose 0.1 gram), or emetine
followed by	*plus*
(2) Diloxanide fuorate,* 500 mg three times per day for 10 days, or diiodohydroxyquin, 650 mg three times per day for 21 days,	(2) Chloroquine, 500 mg (salt) twice per day for two days and then 250 mg twice daily for 26 days,
plus	*plus*
(3) Chloroquine, 500 mg (salt) twice daily for two days and then 250 mg twice daily for 12 days.	(3) Diloxanide furoate,* 500 mg three times per day for 10 days, or diiodohydroxyquin, 650 mg three times per day for 21 days.

*Available in the United States only from the Parasitic Disease Drug Service, Center for Disease Control, Atlanta, GA 30333. Telephone requests may be made by calling (404) 329-3670.

clinically or by laboratory and radiologic tests. When aspiration is indicated, it may provide the definitive diagnosis by detection and isolation of the causative agent. However, in most studies amebas are found in less than 50 percent of probable cases. Though the color of the aspirate is not a useful differentiating feature, the foul odor is characteristic of pyogenic infection but not of amebic abscess. In addition, few polymorphonuclear leukocytes are found in amebic aspirates. Some workers find trophozoites by histologic examination; specimens of wall tissue from the abscess are obtained by doing liver biopsies concurrent with diagnostic aspirations.

The most useful noninvasive test is serologic examination. Almost every patient with an amebic abscess will be serologically positive, and false-positive reactions are rare. Depending on the persistence of antibodies for the test used, a positive reaction in a patient from an endemic area could be misleading, and may only represent past intestinal infection, but not present disease.

Other factors and tests may or may not contribute to the diagnosis because the overlap is great. Patients with pyogenic abscess tend to appear sicker and usually have a higher leukocyte count, whereas patients with an amebic abscess tend to have a right lobe lesion, abnormal findings on chest x-ray studies, pleuritic pain and diarrhea. Results of liver function tests frequently give normal values or show low-grade abnormalities for both conditions, and multiple abscesses may occur for both. If jaundice is present it is more likely due to pyogenic abscess. Blood cultures should be done and may be positive with pyogenic abscess if sepsis is severe. A gallium scan and stool examinations for *E histolytica* should be carried out.

Medical Treatment of Amebic Liver Abscess

Medical treatment is highly effective. Death can usually be prevented if medical treatment (plus aspiration when indicated) is started early enough to prevent rupture. Table 7 lists drugs used to treat all forms of amebiasis according to their site of action as luminal and tissue amebicides.[22] Only metronidazole[23] is effective at both sites; it is, therefore, the drug of first choice for treatment of amebic liver abscess (Table 8). However, because it is not a highly effective luminal amebicide by itself, another luminal drug must also be used, such as diiodohydroxyquin or diloxanide furoate. Because there are occasional failures in treating amebic liver abscess with metronidazole alone, some investigators advocate following it with a two-week course of chloroquine. If metronidazole is not well tolerated, or if parenteral therapy is required, the older and alternate course of treatment is indicated—namely, combined usage of emetine (or dehydroemetine) and chloroquine. The alternate course should also be followed with a luminal amebicide. With either mode of treatment, the patient should show a clinical response within several days. Subsequent radiologic studies will usually show healing of the abscess with slow liver regeneration; generally, healing time ranges from two to ten months.[24] When relapses occur they usually appear within two months.

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